Support for the amendments can be found throughout the specification, the claims and the figures as originally filed. Specifically, support for the amendments to Claims 41 and 45 can be found at least in the specification at page 3, lines 24-25. No new matter has been added to the application by the amendments.

Telephonic Interview

Applicants' Attorneys thanks Examiner Bansal for the helpful telephonic interview of May 8, 2001 in which the rejection of Claims 41, 45 and 64-71 under 35 USC §112, second paragraph in the pending Office Action was discussed. Agreement was reached regarding acceptable language.

Status of Claim 63

Applicants wish to clarify that Claim 63 has not been cancelled and is still pending in the application. An inadvertent typographical error on page 5 of the previous response indicated that Claims 53-63 had been cancelled, rather than Claims 53-62 as correctly indicated throughout the remainder of the response. Therefore, it was clearly never Applicants' intent to cancel Claim 63.

Rejection of Claims 41, 45 and 64-71 Under 35 USC §112, Second Paragraph

During the telephonic interview, language was discussed with the Examiner to further clarify Claims 41 and 45. The agreed upon claim language has been added to Claims 41 and 45, and it is believed that the rejection under 35 USC §112, second paragraph has been obviated. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 41, 45 and 64-71 Under 35 USC §103(a)

Claims 41, 45 and 64-71 stand rejected under 35 USC §103(a) as being unpatentable over Fearnhead *et al.*, "An Interleukin-1β-Converting Enzyme-like Protease is a Common Mediator of Apoptosis in Thymocytes", *FEBS Lett.*, 375: 283-288 (1995).

Specifically, the Examiner states at page 3:

> ...Fearnhead teaches the concept that enhancing caspase activity by agents such as dexamethasone etc. was also directly tied to enhancement of apoptosis in immature thymocytes. Applicant fails to recognize that Fearnhead et al. teaching clearly suggest that apoptosis in immature thymocytes was associated with caspase/procaspase

> activity. Such conclusion was based on the use of known agents that affect caspase/procaspase activity. Though Fearnhead et al. may not teach contacting isolated caspase with an agent and assess its enhancing effect on caspases, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to extend these studies to look for agents that enhance the activity of isolated caspase/procaspase.

Applicants specifically traverse the rejection of the claims for obviousness on the grounds that the teachings of Fearnhead *et al.* do not reasonably suggest a method of enhancing the activity of a procaspase or caspase of the invention, nor a method of identifying an agent which enhances the activity of a procaspase or caspase of the invention, nor the desirability of identifying such an agent.

As described and exemplified extensively throughout the application as filed, in many aspects the claimed invention pertains to the elimination of certain thymocytes via a thymocyte-specific apoptotic mechanism, termed negative selection. The caspase involved in this thymocyte-specific apoptotic mechanism is characterized by its ability to be triggered by TCR stimulation with peptide/MHC, anti-CD3ϵ or other anti-TCR-specific monoclonal antibody, or corticosteroids in thymocytes (see the specification at page 3, lines 16-32). The interleukin-1β-converting enzyme-like protease described by Fearnhead *et al.* is not characterized by its ability to be triggered by TCR stimulation with peptide/MHC, anti-CD3ϵ or other anti-TCR-specific monoclonal antibody, or corticosteroids in thymocytes. Therefore, Fearnhead *et al.* neither teaches nor reasonably suggests that the interleukin-1β-converting enzyme-like protease described is a caspase of the present invention. For that reason, the ordinarily skilled artisan, searching for agents which enhance the activity of a procaspase or caspase of the instant invention would have no motivation to look to the enzyme described by Fearnhead *et al.*

At the time the instant application was filed, much remained to be learned about apoptotic pathways. It was uncertain whether there was a single converging apoptotic pathway or whether there were multiple apoptotic pathways. Moreover, multiple cysteine proteases participating in apoptosis in different pathways in the same cells had been identified. The uncertainty in the art regarding the apoptotic pathway at the time of filing is evidenced by the following excerpt from the teachings of United States Patent No. 5,929,042 (the '042 patent) which was filed on March 3, 1997 (see column 14, lines 49-61):

> The results presented herein argue against the existence of a single "final common pathway" leading to apoptotic cell death. In the two paradigms presented here...the general scheme is similar in that each pathway requires a cysteine aspartase but shows marked selectivity in the specific enzyme required. The differential association of specific cysteine aspartases with apoptosis evoked by different means may account for the proliferation of this family in vertebrates. The utilization of distinct cysteine aspartases by the same cells to promote death from different initiating stimuli raises the possibility that this selectivity can be exploited for the treatment of specific neurodegenerative disorders.

Furthermore, careful review of Fearnhead *et al.* and the instant application evidences the considerable variation between the conditions under which the experimental methods were conducted by the respective researchers. Given the deficiencies in the information available in the art regarding the thymocyte apoptotic pathways at the time the instant application was filed, and the differences in the experimental methods utilized, the ordinarily skilled artisan would not have been able to identify with any reasonable degree of certainty a procaspase or caspase of the invention based on the teachings of Fearnhead *et al.*

Specifically, Fearnhead *et al.* induced apoptosis using a different group of stimuli than that utilized in the exemplification contained in the referenced patent application. Fearnhead *et al.* induced apoptosis using the group of stimuli which includes dexamethasone, a glucocorticoid etoposide, a DNA topoisomerase II inhibitor and thapsigargin (Fearnhead *et al.*, column 2, page 283). In contrast, the apoptosis described in the patent application was induced using the group of stimuli including a peptide/MHC, 2C11 mAb and dexamethasone. Moreover, this group of stimuli are utilized to characterize the procaspase and caspase of the invention (specification, page 3, 29-32). It was well known at the time of filing that different stimuli activate apoptosis differently. Indeed, activation induced by different stimuli can be so varied that the apoptotic modes produced do not even lie on a common pathway (see the excerpt from the '402 patent). This fact is explicitly acknowledged by Fearnhead *et al.* (see column 2, page 283).

Fearnhead *et al.* conducted the experiments described in the reference utilizing *in vitro* suspensions of thymocytes (Fearnhead *et al.*, column 2 page 283). In contrast, the experiments described in the patent application were conducted using a fetal thymocyte organ culture (FTOC), a system which more closely parallels *in vivo* conditions than suspensions of thymocytes (specification, page 10-11,lines 30-33 and 1-8, respectively).

Although Fearnhead *et al.* described utilizing various concentrations of the peptide inhibitor zVAD.fmk, the 200 μM concentration was described as most effective (Fearnhead *et al.*, column 1, page 284). In contrast, the experiments described in the patent application were conducted using a 100 μM concentration of the peptide inhibitor zVAD.fmk (Examples, page 48, line 23). It was well known at the time of filing that the concentration of peptide inhibitors utilized affected the specificity of the reaction.

Moreover, as acknowledged by the Examiner, Fearnhead *et al.* contains no teaching or suggestion directed to isolated enzymes. Thus, Fearnhead *et al.* do not teach or suggest measuring the effect on apoptosis of the enhancement of the activity of an isolated procaspase or caspase, nor identifying an agent which enhances that activity.

Because, given these facts, it must be apparent that the ordinarily skilled artisan could not reasonably identify a procaspase or caspase of the invention utilizing the teachings of Fearnhead *et al.*, the ordinarily skilled artisan would not have had a reasonable expectation of success founded in the cited art of developing a method of identifying an agent which enhances the activity of a procaspase or caspase of the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Correction of Inventorship

On March 13, 2000, Applicants filed an amendment and a petition to correct the inventorship of the present application. Acknowledgment of that correction of inventorship is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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Dated: September 14, 2001

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

41. (Four Times Amended) A method of identifying an agent which enhances the activity of [an] a caspase or procaspase expressed in immature thymocytes, or an active derivative or fragment thereof, wherein said caspase [is necessary for apoptosis] mediates immature thymocyte susceptibility to cell death, comprising the steps of:

(a) contacting an isolated form of a caspase or procaspase expressed in immature thymocytes, or an active derivative or fragment thereof, with a caspase substrate in the presence of the agent; and

(b) identifying enhancement of caspase or procaspase activity.

45. (Four Times Amended) A method of enhancing the activity of [an] a caspase or procaspase expressed in immature thymocytes, or an active derivative or fragment thereof, wherein said caspase [is necessary for apoptosis] mediates immature thymocyte susceptibility to cell death, comprising contacting an isolated form of a caspase or procaspase expressed in immature thymocytes with an agent that enhances the activity of the caspase or procaspase.